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Mortality Patterns Among Workers Exposed to Chloromethyl Ethers—A Preliminary Report

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Chloromethyl methyl ether (CMME) has been used extensively as a crosslinking agent for ion-exchange resins. Commercial grades of CMME are contaminated to the extent of 2–8% with bischloromethyl ether, an alkylating agent which has been shown to be a very potent lung carcinogen in animals. Reports by other investigators in this and other countries have implicated CMME as a lung carcinogen in chemical workers.

The purpose of the study reported here was to examine the lung cancer mortality experience with respect to intensity and duration of exposure in six of the seven chemical companies that account for virtually all of the CMME use in the United States. The study included about 1800 workers who were exposed in the period 1948 to 1972 and abobut 8000 workers not exposed to CMME from the same plants who served as controls. Exposed workers were characterized according to job description and duration of exposure. In several plants the intensity of exposure was numerically graded for each job category with adjustment for temporal changes in the plant processes. Social Security records were used to identify deaths among workers who had left the companies and death certificates have been obtained for virtually all known deaths. The age-adjusted death rate for respiratory cancer in the CMME exposed group as a whole was 2.5 times that in the control group, whereas death rates due to other causes were comparable. There was also a gradation of lung cancer risk according to intensity and duration of exposure and the time elapsed since the onset of exposure.

Although the alkylating agent, chloromethyl methyl ether (CMME), has been produced and used in this country since shortly after World War II as a crosslinking agent for ion-exchange resins and as an intermediate in the production of organic chemicals, it was not until 20 years later that its carcinogenic potential was demonstrated in animals. Beginning in 1968, Van Duuren et al. (*1,2*) reported that CMME was carcinogenic for the mouse skin, and that bischloromethyl ether (BCME), which is an impurity (2–8%) in commercial CMME, was an even more potent carcinogen.

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Since occupational exposures to CMME and BCME were primarily respiratory, an inhalation study was done on rats and hamsters which demonstrated the high potency of BCME for the production of bronchogenic carcinoma and esthesioneuroepitheliomas, even at the very low exposure concentration of 0.1 ppm (*3*).

These findings prompted the follow-up study reported here of workers exposed to CMME and BCME which included six of the seven major producers and users of CMME in the United States; the seventh was studied by investigators from the National Institute for Occupational Safety and Health (*4*). Since these studies were initiated reports of excessive lung cancer mortality among CMME-exposed workers have appeared from this country as well as Germany and Japan (*5–7*). The

14 cases reported by Figueroa (*6*) were independently identified in this study.

Methods

The components of this study included the identification of all workers exposed to CMME in the six firms; the quantification of exposure intensity and duration in several plants; and the selection of a control group of workers at each plant. The Social Security Administration (SSA) files were searched for death records on all workers whose vital status was unknown. Death certificates were obtained on all decedents. Company records were obtained on all past and present employees with known exposure to CMME. The study was confined to males because there were fewer than ten CMME-exposed females. Information was obtained on each worker according to sequential job categories and the associated employment periods for each type of job within the company.

A control group of workers not exposed to CMME was also selected at five of the six firms. The sixth firm had no unexposed males to use as controls. The control group was selected at each firm from among those employed during the time period of exposure for CMME workers and was unselected with respect to specific type of work performed.

In three companies, it was possible to rank the intensity of exposure according to job description. This was done in conference with the production engineers, supervisors and management personnel. The plant processes were reviewed in detail with particular regard to changes made over the years that had obvious effects on the level of exposure. The consensus approach was used to assign an exposure grade of 0.1, 1, 2, 3, 4, 5, or 6 to each job category at various periods of CMME use. It was not possible to assign absolute levels of exposure to any of the grades or to define the relative differences in intensity of exposure between grades or between different companies. Only one plant had quantitative measures of CMME air levels, and these were mostly recent.

The vital status of the workers at the end of 1972 was determined through Social Security records for all those not employed, pensioned or known dead by the companies as of the terminal date. The SSA provided the date of death and the geographical location at death if known; otherwise the last known state of employment or residence was given. As a check on the completeness of SSA records, a sample of about 300 known deaths from two firms was included in the request sent to the SSA.

Death certificates were provided by the firms for most who had died while active employees or pensioners of the firms. Death certificates have been obtained for most of the remaining deaths by requests to local and state bureaus of vital statistics. When a death certificate could not be found in the state listed by the SSA, neighboring states and the state in which the worker obtained his social security number were tried. If these failed, a request was made to the SSA to search for further information on the place of death in their records. Death certificates have now been obtained for 97% of the known deaths. The causes of death are also being verified from hospital and physician records.

For this report, analyses of deaths were confined to respiratory cancer, other cancer, and other causes. Person-years at risk by attained age were used for comparisons of the mortality experience of the CMME-exposed and unexposed workers. The exposed workers entered the table of person-years at risk 1 yr after first exposure and the control workers entered 1 yr after first employment or the date at which CMME was initially used elsewhere in the company, whichever was later. A person remained at risk until date of death or January 1, 1973. A person who was first employed in 1972 or first exposed to CMME in 1972 did not enter the person-years analyses. The comparisons were adjusted for age in 5-yr groupings.

Results

The number of CMME-exposed and control employees in the study from the six plants is shown in Table 1. The table also shows the status of the workers as of the end of 1972. About half were still employed at the firms. About 98% of the exposed and control groups were white, so race was not considered in these analyses.

The check of the completeness of the SSA death records revealed that 94% were correctly identified by the SSA. There were no differences between the two firms whose names of deceased workers were submitted; the SSA

Table 1. Employee status in the exposed (E) and control (C) groups as of January 1, 1973.

Firm	% Employed		% Pensioned		% Separated-Living		% Dead		Total number	
	E	C	E	C	E	C	E	C	E	C
1	55[a]	39	4	5	31	47	10	9	700	1819
2	70	55	6	20	21	9	3	16	204	6411
3	89	52	0	1	10	35	1	12	129	289
4	13	—	0	—	86	—	1	—	204	0
5	20	15	7	0	67	78	6	7	492	81
6	62	40	2	3	35	56	2	1	65	279
Total %	45	51	4	15	45	20	6	14	—	—
Total number	805	4519	76	1348	807	1753	106	1259	1794	8879

[a] Per cent of the total exposed or control group, respectively, at the indicated firm.

Table 2. Person-years at risk by attained age for total elapsed years and for five or more elapsed years since entry into study.

Attained age	1–25 elapsed years		5–25 elapsed years	
	Exposed, %	Control, %	Exposed, %	Control, %
15–24	6.0	3.2	0.7	0.5
25–29	12.7	7.9	7.2	4.4
30–34	16.0	11.7	14.8	10.1
35–39	17.2	14.6	18.4	14.6
40–44	16.3	16.0	18.9	17.1
45–49	12.8	14.5	15.6	16.2
50–54	8.5	11.6	10.9	13.1
55–59	5.3	8.7	6.8	9.8
60–64	2.8	5.9	3.6	6.9
65–69	1.4	3.5	1.9	4.3
70–79	0.8	2.3	1.1	2.8
80–99	0.2	0.1	0.2	0.1
Total	100	100	100	100
Total person-years	21,418	171,454	14,845	136,301

Table 3. Noncancer deaths by age for all workers.

Age	CMME-exposed		Control	
	Deaths	Rate/1000/yr	Deaths	Rate/1000/yr
15–24	3	2.3	3	0.5
25–29	1	0.4	8	0.6
30–34	4	1.2	17	0.8
35–39	5	1.4	32	1.3
40–44	8	0.3	43	1.6
45–49	11	4.0	90	3.6
50–54	7	3.8	104	5.2
55–59	8	7.1	124	8.4
60–64	11	18.3	126	12.4
65–69	7	23.8	173	29.2
70–79	6	34.9	172	44.5
80–99	0	—	18	113.2
Total	71		910	
Age-adjusted rate/1000/yr		3.31		3.35

recovered 94% from each firm, thus suggesting there is probably no bias in the rates of detecting deaths among the firms. The data were further checked for biases due to temporal factors (year of death), age at death, and race, but none were found (chi-square tests, $p > 0.50$ for all comparisons).

Table 2 presents the number of person-years at risk by attained age in the exposed and control groups. The age distribution of the controls is generally older than that of the exposed group, and this accounts for the fact, shown in Table 1, that 6% of the exposed group but 14% of the control group have died.

Only deaths for which the cause of death has been ascertained are included in the analyses. Age-adjusted rates were calculated based on the age distribution of the exposed group. This was done to make the control group more comparable with the exposed workers, who contributed a considerably smaller proportion of person-years beyond the age of 60. Had the control group been used for the age weighting, it would have given considerable weight to the older ages, which were largely irrelevant to the experience of the exposed group.

As shown in Table 3, the two groups had essentially identical death rates due to causes other than cancer, the age-adjusted yearly death rates per 1000 being 3.31 in the CMME-exposed group and 3.35 in the control group.

The age-adjusted death rates from cancer were calculated after excluding the first 4 yr elapsed after initial exposure (or after entry into the study for the control group), in order to avoid inclusion of a large number of exposed cases or person-years who would have had insufficient time to develop cancer. The age-adjusted yearly death rates for all malignant neoplasms other than primary cancer of the respiratory tract were 0.54 and 0.99 per 1000, respectively, as shown in Table 4. The age-specific relative risks between the two groups fluctuated so from one age to another, that the overall difference in nonrespiratory cancer cannot be considered meaningful.

The death rates due to respiratory cancer are shown in Table 5. There were a total of 22 respiratory cancer cases of which 20 were bronchogenic, one was laryngeal and the other mediastinal. The age-adjusted rates were 1.48 in the CMME-exposed group and 0.59 in the control group, and the relative risk adjusted for age (*8*) was 2.53.

At Firm 1, which had the largest number of CMME-exposed employees and most of the respiratory cancer deaths among exposed employees, the age-adjusted relative risk was 2.48 and the rates, shown in Table 6, were 2.40 in the exposed group and 0.97 among controls.

Each person-year contributed by CMME-exposed workers at Firm 1 was characterized by a cumulative exposure score, defined as the sum across all exposure periods up to the middle of that year of the exposure intensity score times the duration, as well as attained age and elapsed years since first exposure. This permitted the calculation of age-adjusted respiratory cancer death rates by cumulative exposure experience for workers having at least 5 yr elapsed since first exposure. Each worker

Table 4. Nonrespiratory cancer deaths by age for workers with ≥5 yr elapsed since entry into the study.

Age	CMME-exposed		Control	
	Deaths	Rate/1000/yr	Deaths	Rate/1000/yr
30–34	0	—	2	0.1
35–39	0	—	4	0.2
40–44	0	—	12	0.5
45–49	0	—	16	0.7
50–54	1	0.6	25	1.4
55–59	4	4.0	23	1.7
60–64	0	—	43	4.6
65–69	1	3.6	36	6.1
70–79	1	6.2	40	10.4
80–99	1	29.4	5	31.4
Total	8		206	
Age-adjusted rate/1000/yr		0.54		0.99

Table 5. Respiratory cancer deaths by age for workers with ≥5 yr elapsed since entry into the study.

Age	CMME-exposed		Control	
	Deaths	Rate/1000/yr	Deaths	Rate/1000/yr
30–34	1	0.5	0	—
35–39	3	1.1	3	0.2
40–44	2	0.7	5	0.2
45–49	3	1.3	14	0.6
50–54	8	5.0	19	1.1
55–59	3	3.0	18	1.3
60–64	0	—	18	1.9
65–69	2	7.2	15	2.5
70–79	0	—	29	7.5
80–99	0	—	1	6.3
Total	22		122	
Age-adjusted rate/1000/yr		1.48		0.59

Table 6. Respiratory cancer deaths by age for workers of Firm 1 with ≥5 yr elapsed since entry into the study.

Age	CMME-exposed		Control	
	Deaths	Rate/1000/yr	Deaths	Rate/1000/yr
30–34	1	0.9	0	—
35–39	3	2.1	2	0.6
40–44	2	1.2	0	—
45–49	3	2.1	5	1.8
50–54	7	7.0	4	1.9
55–59	3	5.4	2	1.5
60–64	0	—	3	3.7
65–69	0	—	3	5.8
70–79	0	—	2	6.0
Total	19		21	
Age-adjusted rate/1000/yr[a]		2.40		0.97

[a] Adjusted to the exposed group at Firm 1.

was also assigned his final cumulative exposure score so that the percentage of respiratory cancer deaths at each exposure level could be calculated. The results are shown in Table 7. There is a clear dose–response relationship between CMME exposure and respiratory cancer.

For further analysis the exposed workers of Firm 1 were grouped into light, medium, and heavy "maximum intensity of exposure" groups—classified by duration of maximum exposure and elapsed years since first exposure—based on their total work experience as shown in Table 8. Similar assignments of person-years by age were also made; here each person-year was classified according to the experience obtained to the middle of that year. All 19 respiratory cancer deaths occurred in those who had been subjected to heavy exposure with 5 yr or more since the onset of exposure; the proportion of workers who died of respiratory cancer increased with the duration of heavy-intensity exposure. The age-adjusted death rates showed a similar increase with duration of exposure.

Cumulative mortality-corrected probabilities of death due to lung cancer for both the non-exposed and BCME-exposed workers at Firm 1 with ≥ 5 yr elapsed since entry into the study (Table 6) and for United States white males (*9*) are plotted on lognormal probability paper as shown in Figure 1. The three lines drawn by eye-fit are parallel supporting the notion that exposure to BCME shortens the time to lung cancer development by a constant factor, roughly 15–20% with respect to the non-exposed workers.

Table 7. Respiratory cancer deaths among CMME-exposed workers of Firm 1 with ≥5 yr elapsed since first exposure by cumulative exposure experience.

Weighted cumulative exposure score[a]	Persons	Lung cancer deaths No.	Lung cancer deaths %	Age-adjusted rate/1000/yr[b]
20–50	40	9	23.1	23.8
12–20	60	3	5.0	2.4
8–12	61	4	6.6	3.5
5–8	57	1	1.8	1.1
3–5	73	1	1.4	1.2
<3	339	1	0.3	0.3
Total	630	19	3.0	

[a] Σ exposure score × years of exposure.
[b] Adjusted to the total exposed group at Firm 1.

Discussion

There is now considerable evidence that BCME and/or CMME are respiratory carcinogens in humans. In this study the relative risk of respiratory cancer for all exposed workers with at least 5 yr elapsed since onset of exposure was 2.5. For those with the heaviest exposure at Firm 1 (12 workers) the relative risk was over 20, i.e., age-adjusted death rate/1000/yr of 23.0 compared to 0.97 for controls; 25% of the most heavily exposed workers (3/12) developed respiratory cancer. A dose-response relationship was also clearly evident.

One distinctive feature of the respiratory cancer experience of the exposed group was the early age at onset. As shown in Table 5, 77% of the respiratory cancers occurred before age 55, whereas if the United States white male rates of respiratory cancer (*9*) are applied to the age-specific person-years at risk in the exposed group, one would expect only 43% to have occurred that early in life. Figure 1 also

Table 8. Respiratory cancer deaths among CMME-exposed workers of Firm 1 by duration and intensity of maximum exposure.

Intensity of maximum exposure (score)	Total duration of maximum exposure, yr	Distribution of Workers by elapsed time since first exposure[a] 0–4 yr	5–9 yr	10–14 yr	15–25 yr	Total for ≥5 yr elapsed ≥5 (%)	Age-Adj. Rate/1000/yr[b]
Heavy (4–6)	≥5	0	1/1	1/1	1/10	3/12 (25)	23.0
	1–5	0	2/3	4/15	6/73	12/91 (13)	8.7
	<1	0	8[c]	27	4/153	4/188 (2.1)	1.5
Medium (2, 3)	≥5	0	0	0	10	0/10	
	1–5	0	11	1	65	0/77	
	<1	0	18	9	85	0/112	
Low (0.1, 1)	≥5	0	1	1	2	0/4	
	1–5	17	13	2	10	0/25	
	<1	52	28	42	41	0/111	

[a] Numerator is number of deaths; denominator is number of workers.
[b] Adjusted to the total exposed group at Firm 1.
[c] Number of workers is given in cells with no deaths.

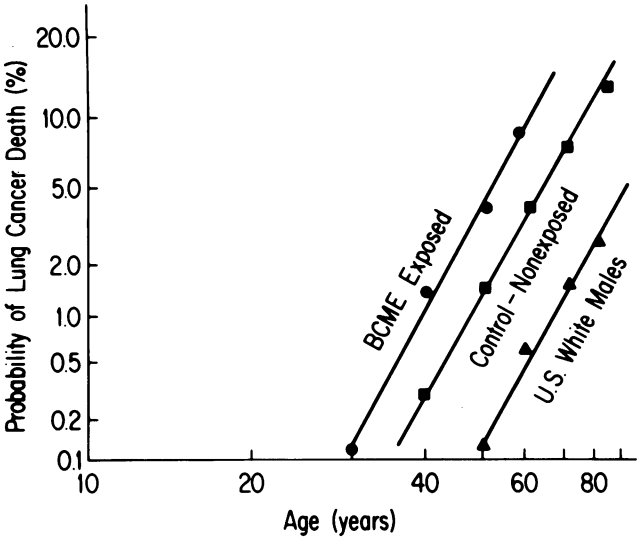

FIGURE 1. Cumulative mortality-corrected probabilities of lung cancer death for BCME-exposed and non-exposed workers at Firm 1 with ≥ 5 yr elapsed since entry into the study and for U.S. white males plotted on lognormal probability paper (lines drawn by eye-fit).

clearly shows the life-shortening effects of CMME exposure with respect to lung cancer. A calculation of the expected years of life lost due to respiratory cancer (*10*) among the 103 workers at Firm 1 with at least 1 yr of heavy exposure (see Table 8) shows that the workers have lost 3.8 yr of life, on the average. If all 291 workers with some heavy exposure are included, the average life-shortening is 1.6 yr. Those who died of respiratory cancer lost an average of 25 yr of life.

The data presented in Table 8 demonstrate that BCME and/or CMME are human respiratory carcinogens within 25 yr of initial exposure if the exposure was very intense. However, it will be important to determine whether further years of follow-up will reveal excessive respiratory cancers in those with lower exposure. An inverse relationship between dose and the length of the latent period is suggested by the observation that the group with heavy exposure of less than one year duration had the longest average latent period.

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